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EXAMINER

LU, FRANK WEI MIN

ART UNIT	PAPER NUMBER
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1634

DATE MAILED: 02/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/806,531

Applicant(s)

ADESSI ET AL.

Examiner

Frank W Lu

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 October 2004 and 18 November 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-18 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-18 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 30 March 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☒ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on October 19, 2004 and November 18, 2004 has been entered. The claims pending in this application are claims 1-18. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the amendment filed on October 19, 2004 and November 18, 2004.

Priority

2. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in European Patent Office on September 30, 1998. It is noted, however, that applicant has not filed a certified copy of this application as required by 35 U.S.C. 119(b).

Response to Arguments

In page 8, second paragraph of applicant's remarks, applicant argues that "[I]n accordance with 37 CFR §1.55(a)(2) and MPEP §201.13(I1)(A), a certified copy of the priority document will be filed before the grant of the patent".

This argument has been fully considered but it is not persuasive toward the withdrawal of the objection since applicant does not submit a certified copy of the priority document.

Drawings

3. The replaced sheet for Figures 1(f) to 1(i) filed on October 19, 2004 has been accepted by the office.

Specification

4. The amendment filed October 19, 2004 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

In page 3, Brief Description of the Drawings, of applicant's remarks, applicant states "[F]igure 4d demonstrates that colonies from different templates do not coincide". However, there is no Figure 4d in the specification.

Applicant is required to cancel the new matter in the reply to this Office Action.

5. The disclosure is objected to because of the following informalities: in page 3, Brief Description of the Drawings, of applicant's remarks, applicant adds several nucleotide sequences having more than 10 nucleotides. However, applicant does not add SEQ ID Nos. for these nucleotide sequences.

Appropriate correction is required.

Claim Objections

6. Claims 2, 3, and 5-18 are objected to because of the following informality: "A method" in line 1 should be "The method".

7. Claim 10 is objected to because of the following informality: "a means" in line 3 should be "means".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 14 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 is rejected because it is unclear that "said solid support" in claim 14 means a solid support in a means for immobilizing the nucleic acid to a solid support in step (1) of claim 1 or a means a solid support in a means for immobilizing the colony primer in step (1) of claim 1 or a solid support in step (2) of claim 1. Please clarify.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1-3, 10-12, 14, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Adams *et al.*, (WO 96/04404, published on February 15, 1996).

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Adams *et al.*, teach method and apparatus for performing amplification of nucleic acid on supports.

Regarding claims 1 and 10, as shown in Figures 1A to 1M, Adams *et al.*, teach a method for performing amplification (ie., PCR) of nucleic acid on supports. As shown in Figures 1A to 1D, since first nucleic acid 23 is double stranded DNA comprising a first strand 25 and a second strand 27 wherein each strand has two target sequences a and b (see page 14, last paragraph) and second nucleic acid 13 is complementary to a of the first strand 25 and serves as a primer (see page 14, last paragraph bridging to page 15, first paragraph), and has a 5' amino group that is covalently bonded to a latex bead (see page 38, claim 4), the terminus of the second nucleic acid 13 that is close to the latex bead is 5' end and the terminus of the first strand 25 that is close to the latex bead is 3' end. Thus the first strand 25 and the second strand 27 are negative strand (a to b is 3' to 5') and positive strand (a to b is 5' to 3') of the first nucleic acid 23 respectively. Since the first nucleic acid is a fragment of a larger nucleic acid sonicated to produce an approximate length of 1 kb (see page 23, fourth paragraph), Adams *et al.*, disclose forming at least one nucleic acid template comprising a nucleic acid to be amplified (ie., the first nucleic acid 23 taught by Adams *et al.*,) wherein the nucleic acid contains an oligonucleotide sequence Y at the 5' end (ie., a of the second strand 27) and an oligonucleotide sequence Z at the 3' end (ie., a of the first strand 25) (see attached Figures 1A to 1D with the examiner's handwritings) as recited in step (1) of claim 1. Since 5' end of the first nucleic acid 23 is phosphate, which is capable to covalently attach to a solid support coated with appropriate chemical groups, Adams *et al.*, disclose that the nucleic acid (ie., the first nucleic acid 23 taught by Adams *et al.*,) carries at the 5' end a means (ie., b of the first strand 25) for immobilizing the nucleic acid to a solid

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support as recited in step (1) of claim 1 wherein the means for immobilizing the nucleic acid template to the solid support comprises a means for immobilizing the nucleic acid sequences covalently to the said support as recited in claim 10. Since the second nucleic acid 13 is immobilized on a latex bead via amino group at 5' end and hybridizes to a of the first strand 25 (see attached Figures 1A to 1D with the examiner's handwritings in previous office action and page 23, last paragraph), Adams *et al.*, disclose mixing the at least one nucleic acid template (ie., the first nucleic acid 23 taught by Adams *et al.*,) with one or more colony primers X (ie., the second nucleic acid 13), each of which (ie., one of multiple identical first nucleic acid 23) can hybridize to the oligonucleotide sequence Z (ie., the second nucleic acid 13) as recited in step (2) of claim 1 wherein the means for immobilizing the colony primers to the solid support comprises a means for immobilizing the nucleic acid sequences (ie., amino group at the 5' end) covalently to the said support as recited in claim 10. Since 5' end of the first nucleic acid 23 are capable to attach to a support (see above) and the second nucleic acid 13 is on a support (see Figures 1A to 1M), Adams *et al.*, disclose that one or more colony primers X (ie., the second nucleic acid 13) carries a means for immobilizing the colony primers to a solid support at the 5' end, in the presence of a solid support (ie., a support for immobilizing the second nucleic acid 13) whereby the 5' ends of both the at least one nucleic acid template (ie., the first nucleic acid 23 taught by Adams *et al.*,) and the colony primers are immobilized to the solid support as recited in step (2) of claim 1. As shown in Figures 1A to 1M, since, after the amplification, the latex beads have multiple copies of a nucleic acid strand (ie., amplification products 31 and 33) (e.g., see page 16), according to the definition of "nucleic acid colony" (see the specification, page 14, last paragraph), Adams *et al.*, disclose performing one or more nucleic acid

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amplification reactions on the immobilized nucleic acid template (ie., the first nucleic acid 23 taught by Adams *et al.*,) so that nucleic acid colonies are generated as recited in step (3) of claim 1.

Regarding claim 2, since, in the first nucleic acid taught by Adams *et al.*, a of the second strand 27 is an oligonucleotide sequence Y at the 5' end while a of the first strand 25 is an oligonucleotide sequence Z at the 3' end (see above), and a of the second strand 27 or the second nucleic acid 13 is complementary to a of the first strand 25 (see attached Figures 1A to 1D with the examiner's handwritings), Adams *et al.*, disclose that the oligonucleotide sequence Z (ie., a of the first strand 25) is complementary to oligonucleotide sequence Y (ie., a of the second strand 27) and colony primer X (ie., the second nucleic acid 13) is of the same sequence as oligonucleotide sequence Y as recited in claim 2.

Regarding claim 3, since, in the first nucleic acid taught by Adams *et al.*, a of the second strand 27 is an oligonucleotide sequence Y at the 5' end while a of the first strand 25 is an oligonucleotide sequence Z at the 3' end (see above), and a of the second strand 27 or the second nucleic acid 13 is complementary to a of the first strand 25, and the third nucleic acid 15 taught by Adams *et al.*, is complementary to b of the second strand 27 (see attached Figures 1A to 1D with the examiner's handwritings and page 15, first paragraph), Adams *et al.*, disclose that two different colony primers X (ie., the second nucleic acid 13 and the third nucleic acid 15) are mixed with the at least one nucleic acid template (ie., the first nucleic acid 23) in step (2) of claim 1 and wherein one of the sequences of colony primers X (ie., the second nucleic acid 13) can hybridize to the oligonucleotide sequence Z (ie., a of the first strand 25) and the

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oligonucleotide sequence Y (ie., a of the second strand 27) is the same as the sequence of one of the colony primers X as recited in claim 3.

Regarding claims 11 and 12, since Adams *et al.*, teach that the second nucleic acid 13 has a 5' amino group (see page 23, last paragraph) and 5' end of the first nucleic acid 23 is phosphate, Adams *et al.*, disclose that said means for immobilizing the nucleic acid sequences covalently to the solid support is a chemically modifiable functional group (ie., amino group or phosphate group) as recited in claim 11 wherein said chemically modifiable functional group is a phosphate group, a carboxyl or aldehyde moiety, a thiol, a hydroxyl, a dimethoxytrityl (DMT), or an amino group as recited in claim 12.

Regarding claims 14 and 15, since the support is a glass bead (see page 7, first paragraph), claims 14 and 15 are anticipated by Adams *et al.*.

Therefore, Adams *et al.*, (1996) teach all limitations recited in claims 1-3, 10-12, 14, and 15.

Response to Arguments

In page 12, fifth paragraph bridging to page 14, fifth paragraph of applicant's remarks, applicant argues that "[A]dams *et al.*, does not teach step (2) of applicants' claimed method, in which colony primers are mixed with nucleic acid templates in the presence of a solid support 'whereby the 5' ends of both the nucleic acid template and the colony primers are immobilized to the solid support'. In particular, Adams does not show a method in which nucleic acid templates are 'immobilized to the solid support' (step (2) of applicants' claim) prior to the step of 'performing one or more nucleic acid amplification reactions' on the nucleic acid templates (step (3) of applicants' claim)".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. Since Adams *et al.*, teach to hybridize nucleic acid templates to primers that are immobilized on a support before amplification (see above and Figure 1D), both the nucleic acid templates and primers must be on the support before the amplification starts. Therefore, Adams *et al.*, disclose that nucleic acid templates are immobilized to the solid support (step (2) of applicants' claim) prior to the step of performing one or more nucleic acid amplification reactions on the nucleic acid templates whereby the 5' ends of both the nucleic acid template and the colony primers are immobilized to the solid support.

12. Claims 1-3, 10-12, 14, 15, and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by Adams *et al.*, (US Patent No. 6,060,288, filed on February 14, 1997).

Adams *et al.*, teach method for performing amplification of nucleic acid on supports.

Regarding claims 1, as shown in Figures 1A to 1M, Adams *et al.*, teach a method for performing amplification (ie., PCR) of nucleic acid on supports. As shown in Figures 1A to 1D, since first nucleic acid 23 is double stranded DNA comprising a first strand 25 and a second strand 27 wherein each strand has two target sequences a and b and second nucleic acid 13 is complementary to a of the first strand 25 and serves as a primer (see column 8, lines 52-65), and has a 5' amino group that is covalently bonded to a latex bead (see column 22, lines 48-56), the terminus of the second nucleic acid 13 that is close to the latex bead is 5' end and the terminus of the first strand 25 that is close to the latex bead is 3' end. Thus the first strand 25 and the second strand 27 are negative strand (a to b is 3' to 5') and positive strand (a to b is 5' to 3') of the first nucleic acid 23 respectively. Since the first nucleic acid is a fragment of a larger nucleic

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acid sonicated to produce an approximate length of 1 kb (see column 22, lines 42-46), Adams *et al.*, disclose forming at least one nucleic acid template comprising a nucleic acid to be amplified (ie., the first nucleic acid 23 taught by Adams *et al.*,) wherein the nucleic acid contains an oligonucleotide sequence Y at the 5' end (ie., a of the second strand 27) and an oligonucleotide sequence Z at the 3' end (ie., a of the first strand 25) (see attached Figures 1A to 1D with the examiner's handwritings) as recited in step (1) of claim 1. Since 5' end of the first nucleic acid 23 is phosphate, which is capable to covalently attach to a solid support coated with appropriate chemical groups, Adams *et al.*, disclose that the nucleic acid (ie., the first nucleic acid 23 taught by Adams *et al.*,) carries at the 5' end a means (ie., b of the first strand 25) for immobilizing the nucleic acid to a solid support as recited in step (1) of claim 1 wherein the means for immobilizing the nucleic acid template to the solid support comprises a means for immobilizing the nucleic acid sequences covalently to the said support as recited in claim 10. Since the second nucleic acid 13 is immobilized on a latex bead via amino group at 5' end and hybridizes to a of the first strand 25 (see attached Figures 1A to 1D with the examiner's handwritings in previous office action and column 22, lines 48-56), Adams *et al.*, disclose mixing the at least one nucleic acid template (ie., the first nucleic acid 23 taught by Adams *et al.*,) with one or more colony primers X (ie., the second nucleic acid 13), each of which (ie., one of multiple identical nucleic acid 23) can hybridize to the oligonucleotide sequence Z (ie., the second nucleic acid 13) as recited in step (2) of claim 1 wherein the means for immobilizing the colony primers to the solid support comprises a means for immobilizing the nucleic acid sequences (ie., amino group at the 5' end) covalently to the said support as recited in claim 10. Since 5' end of the first nucleic acid 23 and the second nucleic acid 13 are capable to attach to a support (see above) and the second

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nucleic acid 13 is on a support (see Figures 1A to 1M), Adams *et al.*, disclose that one or more colony primers X (ie., the second nucleic acid 13) carries a means for immobilizing the colony primers to a solid support at the 5' end, in the presence of a solid support (ie., a support for immobilizing the second nucleic acid 13) whereby the 5' ends of both the at least one nucleic acid template (ie., the first nucleic acid 23 taught by Adams *et al.*,) and the colony primers are immobilized to the solid support as recited in step (2) of claim 1. As shown in Figures 1A to 1M, since, after the amplification, the latex beads have multiple copies of a nucleic acid strand (ie., amplification products 31 and 33) (e.g., see column 9), according to the definition of "nucleic acid colony" (see the specification, page 14, last paragraph), Adams *et al.*, disclose performing one or more nucleic acid amplification reactions on the immobilized nucleic acid template (ie., the first nucleic acid 23 taught by Adams *et al.*,) so that nucleic acid colonies (ie., multiple amplification products 31 and 33) are generated as recited in step (3) of claim 1.

Regarding claim 2, since, in the first nucleic acid taught by Adams *et al.*, a of the second strand 27 is an oligonucleotide sequence Y at the 5' end while a of the first strand 25 is an oligonucleotide sequence Z at the 3' end (see above) and a of the second strand 27 or the second nucleic acid 13 is complementary to a of the first strand 25 (see attached Figures 1A to 1D with the examiner's handwritings), Adams *et al.*, disclose that the oligonucleotide sequence Z (ie., a of the first strand 25) is complementary to oligonucleotide sequence Y (ie., a of the second strand 27) and colony primer X (ie., the second nucleic acid 13) is of the same sequence as oligonucleotide sequence Y as recited in claim 2.

Regarding claim 3, since, in the first nucleic acid taught by Adams *et al.*, a of the second strand 27 is an oligonucleotide sequence Y at the 5' end while a of the first strand 25 is an

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oligonucleotide sequence Z at the 3' end (see above) and a of the second strand 27 or the second nucleic acid 13 is complementary to a of the first strand 25, and the third nucleic acid 15 taught by Adams *et al.*, is complementary to b of the second strand 27 (see attached Figures 1A to 1D with the examiner's handwritings and column 8, lines 52-65), Adams *et al.*, disclose that two different colony primers X (ie., the second nucleic acid 13 and the third nucleic acid 15) are mixed with the at least one nucleic acid template (ie., the first nucleic acid) in step (2) and wherein one of the sequences of colony primers X (ie., the second nucleic acid 13) can hybridize to the oligonucleotide sequence Z (ie., a of the first strand 25) and the oligonucleotide sequence Y (ie., a of the second strand 27) is the same as the sequence of one of the colony primers X.

Regarding claims 11 and 12, since Adams *et al.*, teach that the second nucleic acid 13 has a 5' amino group (see column 22, lines 48-56) and 5' end of the first nucleic acid 23 is phosphate, Adams *et al.*, disclose that said means for immobilizing the nucleic acid sequences covalently to the solid support is a chemically modifiable functional group (ie., amino group or phosphate group) as recited in claim 11 wherein said chemically modifiable functional group is a phosphate group, a carboxyl or aldehyde moiety, a thiol, a hydroxyl, a dimethoxytrityl (DMT), or an amino group as recited in claim 12.

Regarding claims 14 and 15, since the support is a glass bead (see column 7, lines 41-52), claims 14 and 15 are anticipated by Adams *et al.*.

Regarding claim 17, the density of colony primers X attached to the solid support is at least 1 fmol/mm² (see column 27, lines 50-55).

Therefore, Adams *et al.*, (1997) teach all limitations recited in claims 1-3, 10-12, 14, 15, and 17.

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Response to Arguments

In page 14, sixth paragraph bridging to page 15, fourth paragraph of applicant's remarks, applicant argues that "[A]dams *et al.*, does not teach step (2) of applicants' claimed method, in which colony primers are mixed with nucleic acid templates in the presence of a solid support 'whereby the 5' ends of both the nucleic acid template and the colony primers are immobilized to the solid support'. In particular, Adams does not show a method in which nucleic acid templates are 'immobilized to the solid support' (step (2) of applicants' claim) prior to the step of 'performing one or more nucleic acid amplification reactions' on the nucleic acid templates (step (3) of applicants' claim)".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. Since Adams *et al.*, teach to hybridize nucleic acid templates to primers that are immobilized on a support before amplification (see above and Figure 1D), both the nucleic acid templates and primers must be on the support before the amplification starts. Therefore, Adams *et al.*, disclose that nucleic acid templates are immobilized to the solid support (step (2) of applicants' claim) prior to the step of performing one or more nucleic acid amplification reactions on the nucleic acid templates whereby the 5' ends of both the nucleic acid template and the colony primers are immobilized to the solid support.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

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having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Adams *et al.*, (1996) as applied to claims 1-3, 10-12, 14, and 15 above, and further in view of Huang (US Patent No. 5,645,994, filed on June 6, 1995).

The teachings of Adams *et al.*, have been summarized previously, *supra*.

Regarding claim 4, since claim 1 of this instant application teach all limitations of claim 4 except one or more degenerate colony primer X, as shown above and Adams *et al.*, teach all limitations of claim 1 (see above), Adams *et al.*, disclose all limitations of claim 4 except one or more degenerate colony primer X.

Huang teaches the advantages of the universal primers (ie., degenerate colony primer X), which are: (1) identification of a plurality of species from one sample; and (2) that, by analysis of a sufficient number of the individual amplified molecules, substantially all of the species present in the original sample would be detected and identified (see column 5, fourth and fifth paragraphs).

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Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 4 in view of the patents of Adams *et al.*, and Huang. One having ordinary skill in the art would have been motivated to do so because Huang has successfully used one or more universal primers (ie., degenerate colony primer X) in an amplification reaction and use of the universal primers (ie., degenerate colony primer X) in an amplification reaction would permit identification of a plurality of species from one sample, and, by analysis of a sufficient number of the individual amplified molecules, substantially all of the species present in the original sample would be detected and identified (see column 5, fourth and fifth paragraphs). One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to perform a method recited in claim 4 using one or more universal primers (ie., degenerate colony primer X).

15. Claims 5, 6, 8, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adams *et al.*, (1996) as applied to claims 1-3, 10-12, 14, and 15 above, and further in view of Bukh *et al.*, (US Patent No. 5,514,539, published on May 7, 1996).

The teachings of Adams *et al.*, have been summarized previously, *supra*.

Regarding claims 8 and 9, since Adams *et al.*, teach that biotinylated amplification products are detected by analyzing the conversion of a chemiluminescent substrate by a streptavidin-alkaline phosphatase conjugate using X-ray film or a microscopy (see page 25, third paragraph), Adams *et al.*, disclose visualizing the nucleic acid colonies wherein said visualization step involves the use of a labeled nucleic acid probe as recited in claims 8 and 9.

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Adams *et al.*, do not disclose to perform an additional sequence determination step as recited in claim 5 wherein the sequence determination step involves the incorporation and detection of labeled nucleotides as recited in claim 6.

Bukh *et al.*, teach that the amplification products of PCR are detected either directly or indirectly (see column 17, last paragraph bridging to column 18, first paragraph).

Regarding claims 5 and 6, Bukh *et al.*, teach the direct detection of the amplification products is carried out using one or more labeled dNTPs. The labeled amplified PCR products are also detected via direct sequencing of the PCR-products (see column 17, last paragraph bridging to column 18, first paragraph). Thus Bukh *et al.*, disclose to perform an additional sequence determination step as recited in claim 5 wherein the sequence determination step involves the incorporation and detection of labeled nucleotides as recited in claim 6.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed an additional sequence determination step as recited in claim 5 wherein the sequence determination step involves the incorporation and detection of labeled nucleotides as recited in claim 6 in view of the patents of Adams *et al.*, and Bukh *et al.*. One having ordinary skill in the art would have been motivated to do so because Bukh *et al.*, have successfully detected PCR products via direct sequencing of the PCR-products and the simple replacement of one well known method (i.e., the method taught by Adams *et al.*,) from another well known method (i.e., detection of PCR products via direct sequencing of the PCR-products taught by Bukh *et al.*,) during the process of detecting labeled PCR products would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the detection

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method for PCR products taught by Adams *et al.*, and the detection method for PCR products taught by Bukh *et al.*, are functional equivalent methods which are used for the same purpose (see Bukh *et al.*, column 17, last paragraph bridging to column 18, first paragraph).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06.

16. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Adams *et al.*, (1996) in view of Bukh *et al.*, (1996) as applied to claims 1-3, 5, 6, 8-12, 14, and 15 above, and further in view of Hildebrand *et al.*, (US Patent No. 6,287,764 B1, priority date: February 11, 1998).

The teachings of Adams *et al.*, and Bukh *et al.*, have been summarized previously, *supra*. Adams *et al.*, and Bukh *et al.*, do not disclose that the full or partial sequences of amplified nucleic acid templates present in more than one nucleic acid colony are determined simultaneously as recited in claim 7.

Hildebrand *et al.*, teach simultaneous sequencing of 10 PCR products (see column 11, last paragraph bridging to column 12, first paragraph) (determination of the full or partial sequences of the amplified nucleic acid templates as recited in claim 7).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have simultaneously determined the full or partial sequences of the amplified nucleic acid templates present in more than one nucleic acid colony

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in view of the patents of Adams *et al.*, Bukh *et al.*, and Hildebrand *et al.*. One having ordinary skill in the art would have been motivated to do so because Hildebrand *et al.*, have successfully simultaneously sequenced 10 PCR products and simultaneously determining the full or partial sequences of the amplified nucleic acid templates present in more than one nucleic acid colony would save time and laboratory cost. One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to simultaneously determine the full or partial sequences of the amplified nucleic acid templates present in more than one nucleic acid colony as recited in claim 7.

17. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Adams *et al.*, (1996) as applied to claims 1-3, 10-12, 14, and 15 above, and further in view of Lund *et al.*, (Nucleic Acids Research, 16, 10861-10880, 1988).

The teachings of Adams *et al.*, have been summarized previously, *supra*.

Adams *et al.*, do not disclose that a mean for attaching the nucleic acid at the 5' end of the nucleic acid template is an amino group as recited in claim 13.

Lund *et al.*, teach that 5'-phosphate group or 5' amino group of a nucleic acid is used to attach the nucleic acid to a solid support (see page 10861, abstract).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have made a nucleic acid template with an amino group at its 5' end as recited in claim 13 in view of the prior art of Adams *et al.*, and Lund *et al.*. One having ordinary skill in the art would have been motivated to do so because Lund *et al.*, have successfully attached a nucleic acid with an amino group at its 5' end and a nucleic acid using its

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5' phosphate onto a solid support and the simple replacement of a means for immobilizing the nucleic acid to a solid support (i.e., 5'-phosphate taught by Adams *et al.*,) from another means for immobilizing the nucleic acid to a solid support (i.e., 5'-amino group taught by Lund *et al.*,) during the process of making a nucleic acid template recited in claim 13 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the replacement would not change the method step of claim 13.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements in such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

18. Claims 16 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adams *et al.*, (1996) as applied to claims 1-3, 10-12, 14, and 15 above, and further in view of Fodor *et al.*, (US Patent No. 5,800,992, filed on June 25, 1996).

The teachings of Adams *et al.*, have been summarized previously, *supra*.

Adams *et al.*, do not disclose that the density of the nucleic acid colonies is 10,000/mm² to 100,000/mm² as recited in claim 16 and the density of the nucleic acid templates is 10,000/mm² to 100,000/mm² as recited in claim 18.

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Fodor *et al.*, teach to make a support immobilized with a nucleic acid wherein the density of the nucleic acid templates is 10,000/mm² to 100,000/mm² (see column 7, last paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have made a support immobilized with a nucleic acid wherein the density of the nucleic acid templates is 10,000/mm² to 100,000/mm² as recited in claim 18 and used the nucleic acid in this support to generate the nucleic acid colonies at a density of 10,000/mm² to 100,000/mm² as recited in claim 16 in view of the patents of Adams *et al.*, and Fodor *et al.*. One having ordinary skill in the art would have been motivated to do so because Fodor *et al.*, have successfully made a support immobilized with a nucleic acid wherein the density of the nucleic acid templates is 10,000/mm² to 100,000/mm². One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to make a support immobilized with a nucleic acid wherein the density of the nucleic acid templates is 10,000/mm² to 100,000/mm² as recited in claim 18 and use the nucleic acid in this support to generate the nucleic acid colonies at a density of 10,000/mm² to 100,000/mm² as recited in claim 16.

Response to Arguments

In page 15, fifth paragraph bridging to page 19, third paragraph of applicant's remarks, applicant argues that: (1) "Nor does Adams *et al.* provide any motivation to alter the disclosed method along the lines of the applicants' invention, by immobilizing the nucleic acid template to the solid support"; (2) "[B]ecause the method of Adams *et al.* is intended to indicate when a target sequence is absent from a sample, there would clearly be no reason to immobilize the target sequence to the support since this would produce a false positive result, indicating that the

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target sequence was present”; (3) “[T]he secondary references, discussed briefly below, were cited for their disclosure of various individual features not recited in independent claim 1.

However, none of these references make up for the deficiencies of the primary reference(s) with respect to the applicants' independent claims. That is, none of them discloses or suggests an amplification method in which a nucleic acid template and primers are immobilized to a solid support prior to amplification. Therefore, the combination of any or all of these references with Adam *et al.* does not disclose or suggest the claimed amplification method”; and (4) “the ‘universal primers’ in Huang are not in fact fully degenerate primers”.

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, Adam *et al.*, teach an amplification method in which a nucleic acid template and primers are immobilized to a solid support prior to amplification (see above Response to Arguments on the rejection under 35 U.S.C 102). Second, claim 4 does not require that degenerate colony primers are fully degenerate as argued by applicant.

Conclusion

19. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period

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will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

20. No claim is allowed.

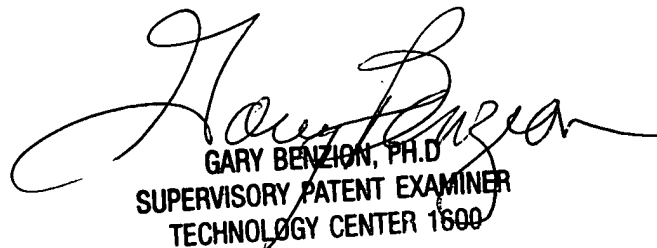
21. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (571)272-0745.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
PSA
February 15, 2005


GARY BENZION, PH.D.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600